

**REMARKS**

In the present Amendment, claim 1 has been amended to correct a typographical error. New claims 30-34 have been added. Section 112 support for claim 30 may be found, for example, at pages 13-17, Examples 1-4 of the specification. Section 112 support for claims 31-34 may also be found in the working Examples. See Examples 1-4 at pages 13-17, including Tables 1 and 2.

No new matter has been added, and entry of the Amendment is respectfully requested.

Upon entry of the Amendment, claims 1-34 will be pending.

In Paragraph No. 4 of the Action, claims 1-29 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zhao US 2002/0091251 A1 in combination with Tomihata et al, Journal of Biomedical Materials Research (1997), Vol. 37, Pages 243-251.

Applicants submit this rejection should be withdrawn because Zhao '251 and Tomihata et al do not disclose or render obvious the method for producing the double-crosslinked hyaluronate material of the present invention, alone or in combination.

Claim 1 recites a method for producing a double-crosslinked hyaluronate material, comprising the steps of:

(a) subjecting hyaluronic acid or a salt thereof to a first crosslinking reaction using either **an epoxide compound or a carbodiimide compound** as a crosslinking agent, and

(b) subjecting the product obtained from step (a) to a second crosslinking reaction using **either an epoxide compound as a crosslinking agent if a carbodiimide compound was used as the crosslinking agent in step (a), or using a carbodiimide compound as a crosslinking**

**agent if an epoxide compound was used as the crosslinking agent in step (a), thereby**  
obtaining a double crosslinked hyaluronate material.

The method of the invention uses a carbodiimide compound and an epoxide compound as crosslinking agents in a two-step crosslinking reaction, respectively. The Examiner will note that the method of the invention uses only a carbodiimide and an epoxide as crosslinking agents, and the first and second crosslinking reactions use different crosslinking agents.

The rejection of claims 1-29 relies on Zhao and Tomihata et al for the teaching of **crosslinked HA derivatives**. Zhao teaches double crosslinking in a step-wise manner with the same or different crosslinking agent. See paragraph 27 of Zhao. Zhao further discloses numerous crosslinking agents including carbodiimide and epoxy crosslinkers (see paragraph 19 and claims 4 and 5).

Applicants respectfully submit that Zhao does not explicitly teach or suggest HA crosslinked derivatives **using the combination of a carbodimide and an epoxide as crosslinking agents**. In this regard, Zhao discloses that carbodiimide and epoxide may serve as crosslinking agents, but Zhao also discloses several other crosslinking agents. Second, Zhao teaches away from the present invention in that the first and the second crosslinking reactions may use the same crosslinking agent (see Table 1). Zhao also fails to teach or suggest that the first and the second crosslinking reaction using different crosslinking agent diversely of the invention, such as carbodiimide or epoxide. Therefore, there is no motivation and no reasonable expectation of success for achieving the method for producing a double crosslinked HA material as recited in present claim 1.

Tomihata et al disclose a specific carbodiimide; however, the combination of Zhao with Tomihata still fails to teach or suggest the method as recited in claim 1.

**The claimed invention provides unexpectedly superior results**

As a separate and independent basis for the patentability of the pending claims, Applicants submit that the claimed invention provides an unexpectedly superior extinction ratio in comparison to Zhao.

Zhao discloses that the double crosslinked HA has better biostability than the single crosslinked HA. See Table 4 of the Zhao, where the double crosslinked HA (CHA-17) degrades about 1.45%, and the single crosslinked HA (CHA-16) degrades about 10.45%. That the double crosslinked HA of the present invention degrades only 0.08-0.35% is unexpected in view of Zhao. See Examples 1-4 of the invention. CHA-17 of Zhao uses 1, 2, 7, 8-diepoxyoctane as a crosslinking agent in both the first and second crosslinking reactions; in contrast, Examples 1-4 of the present invention use a carbodiimide or an epoxide in the first and second crosslinking reactions, respectively.

The comparison of the double crosslinked HA degradation is tabulated below:

	Experimental No.	HA degradation
Present invention	Example 1	0.08%
Present invention	Example 2	0.35%
Present invention	Example 3	0.12%
Present invention	Example 4	0.15%
US 2002/0091251 A1	CHA-17	~1.45%

The above advantages achieved by the invention are unappreciated and unexpected from the teachings of Zhao.

As the cited reference (Zhao) does not teach or suggest the feature as set forth in present claim 1, it is Applicants' belief that claim 1 is allowable over Zhao and Tomihata et al. Insofar as claims 2-31 depend from claim 1, it is Applicants' belief that these claims are also allowable at least by virtue of their dependency.

**New claims 30-34**

Applicants submit that new claims 30 and 31 are novel and non-obvious over the Zhao and Tomihata et al for the additional reasons discussed below.

The method of claim 30 recites the order of the crosslinking agents used. The Examiner will note that the degradation rate of the product is affected by the order of the crosslinking agents used. Example 1 of the application utilizes a carbodiimide (EDC) as the first crosslinking agent, and an epoxide (EGDGE) as the second crosslinking agent. Examples 2-4 utilize an epoxide (EGDGE) as the first crosslinking agent, and a carbodiimide (EDC) as the second crosslinking agent. As a result, Example 1 only degrades 0.08%; however, Examples 2-4 degraded 0.12-0.35%, respectively. Accordingly, HA is better crosslinked by the carbodiimide (EDC) at first, and then crosslinked by the epoxide (EGDGE).

Applicants submit that new claim 31 is novel and non-obvious over Zhao and Tomihata et al for the reasons discussed below.

The method of claim 31 recites that the crosslinking reaction is performed in a mixed solvent including an organic solvent and water. This unique feature may prevent the production

Amendment Under 37 C.F.R. § 1.116  
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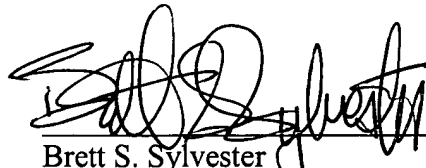
of side products during the crosslinking reaction. Zhao and Tomihata et al, either alone or in combination, do not teach or suggest the use of a mixed solvent including an organic solvent and water for the crosslinking reaction. Zhao and Tomihata et al also fail to teach or suggest that the organic solvent of the mixed solvent is acetone, and the volume ratio of the organic solvent to the mixed solvent.

In view of above, reconsideration and withdrawal of the §103(a) rejection based on Zhao and Tomihata et al are respectfully requested.

Allowance is respectfully requested. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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